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REVIEW

OPEN

Infections in decompensated cirrhosis: Pathophysiology, management, and research agenda

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Abstract

Bacterial infections in patients with cirrhosis lead to a 4-fold increase in mortality. Immune dysfunction in cirrhosis further increases the risk of bacterial infections, in addition to alterations in the gut microbiome, which increase the risk of pathogenic bacteria. High rates of empiric antibiotic use contribute to increased incidence of multidrug-resistant organisms and further increases in mortality. Despite continous advances in the field, major unknowns regarding interactions between the immune system and the gut microbiome and strategies to reduce infection risk and improve mortality deserve further investigation. Here, we highlight the unknowns in these major research areas and make a proposal for a research agenda to move toward improving disease progression and outcomes in patients with cirrhosis and infections.

Key Words: bacterial infections, cirrhosis, gut-liver axis, multi-drug resistant organisms

KEY POINTS

- Bacterial infections are a frequent complication in patients with cirrhosis, leading to a higher risk of developing organ failures and a 4-fold increase in the risk of death.
- Immune dysfunction, gut barrier abnormalities, and impairment of gut microbiome composition and function play a key role in the increased susceptibility to bacterial infections in patients with cirrhosis.
- The diagnosis of bacterial infections in patients with decompensated cirrhosis can be challenging, and

Abbreviations: ACLF, acute-on-chronic liver failure; CLIF, Chronic Liver Failure Consortium; DC, dendritic cells; EASL, European Association for the Study of the Liver; FMT, fecal microbiota transplant; MDRO, multidrug-resistant organism; MRSA, methicillin-resistant *Staphylococcus aureus*; PD-L1, programmed cell death ligand; qSOFA, quickSOFA; SBP, spontaneous bacterial peritonitis; SOFA, sequential organ failure assessment score; VRE, vancomycin-resistant enterococci.

Jessica Ferguson Toll and Elsa Solà are co-first authors.

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better biomarkers are needed for earlier identification and prognostic stratification.
- Despite progressive improvement in the management of bacterial infections, mortality remains high, and the risk of MDROs is a concern in this vulnerable population. Further knowledge is needed to optimize antibiotic treatment, prevention strategies, decrease the risk of MDROs, and improve prognosis.
- Despite continous advances in the field, major unknowns remain that deserve further investigation. Here, we highlight the unknowns in the major research areas and make a proposal for a research agenda to move toward improving the early identification, management, and outcomes of patients with cirrhosis and infections.

INTRODUCTION

Chronic liver disease leading to cirrhosis is a common condition. A recent population-based study reported that 2.8% of civilian US adults have evidence of advanced liver fibrosis.[1] Another estimated that approximately a tenth of those (0.27%, n = 633,000) have cirrhosis.[2] As of 2020, the CDC reported 57,000 subjects succumbed to cirrhosis, which suggests a nearly 10% annual fatality rate among those with cirrhosis.[3] Severe hepatic decompensation in end-stage liver disease may lead to concomitant dysfunction and failure of the liver and nonhepatic organ systems, known as acute-on-chronic liver failure (ACLF), with mortality rates as high as 50%.[4,5]

Systemic infection, including sepsis, is an important determinant of outcomes in patients with cirrhosis. Sepsis is common, occurring in 5%–20% of patients hospitalized with cirrhosis; it is even more prevalent among patients with ACLF.[6] Bacterial infections frequently lead to organ failure in patients with cirrhosis and are the most common precipitating factor of ACLF.[7,8] Almost 50% of patients with cirrhosis and bacterial infections develop ACLF during their hospitalization.[9] In addition, up to 34% of infections in cirrhosis are due to multidrug-resistant organisms (MDROs), which further increases mortality.[6]

Immune dysfunction plays a significant role in the risk of a variety of infectious complications associated with decompensated cirrhosis. The extent to which immune dysfunction results in increased incidence of infection and the interplay between immune responses and gut microbiome are topics of great interest to help identify high-risk patients and develop new prevention and therapeutic strategies to decrease both rates of infection and mortality. This is coupled with the clinical difficulty of rapidly identifying infections in decompensated cirrhosis and initiating appropriate antimicrobial therapy in a timely fashion.

Despite significant research in this area, the questions of defining infection risk factors, diagnosing infections, and mitigating risk factors remain unanswered. In this opinion article, we summarize the relevant literature related to the immunologic and microbiome changes which occur in cirrhosis, as well as the infection risk and complexity in diagnosis and management, while highlighting the unknowns in these areas. Finally, we make a proposal for a research agenda that can guide and expedite research in the field to move toward improving the management and outcomes of patients with cirrhosis and bacterial infections.

PATHOGENESIS

Cirrhosis is associated with multiple internal and external factors that increase the susceptibility to develop bacterial infections (Figure 1). The major inherent factors to patients with cirrhosis are cirrhosis-associated immune dysfunction, impaired gut permeability, and changes in microbiome and function.

Effects of cirrhosis-associated immune dysfunction

Cirrhosis-associated immune dysfunction is characterized by a wide range of immune abnormalities affecting most of the immune cell compartments at the systemic and intrahepatic levels (Figure 1).[10] Immune dysfunction is dynamic and includes progressive systemic inflammation and immune cell activation, together with features of immunosuppression. The presence of systemic inflammation is supported by an increase in acute-phase proteins (such as C-reactive protein), cytokines (ie, IL-6, TNFa, and IL-1B) and endothelial activation markers (ie, vascular cell adhesion molecule 1, intracellular adhesion molecule 1, and VEGF). The magnitude of the systemic inflammation increases in parallel with the severity of the disease, from compensated to decompensated cirrhosis and is markedly intense in patients with ACLF.[11,12] In addition, the immune cell responses involving the innate and adaptive compartments are markedly impaired, affecting most cell subsets (Table 1).[10,13] Activation of immune cells is mainly characterized by activated neutrophils, monocytes expressing activation markers (HLA-DR, CD80, and CD86), and interferon-gamma–expressing T cells.

However, despite marked immune cell activation, cirrhosis progression is associated with features of immunosuppression. Many studies have shown that monocytes and neutrophils show defective function including impaired phagocytosis and chemotaxis, which are key for microorganism killing.[13,14] Immunodeficiency is also dynamic and parallels the progression of the disease. In advanced cirrhosis, and particularly in ACLF, there is an expansion of immunosuppressor and

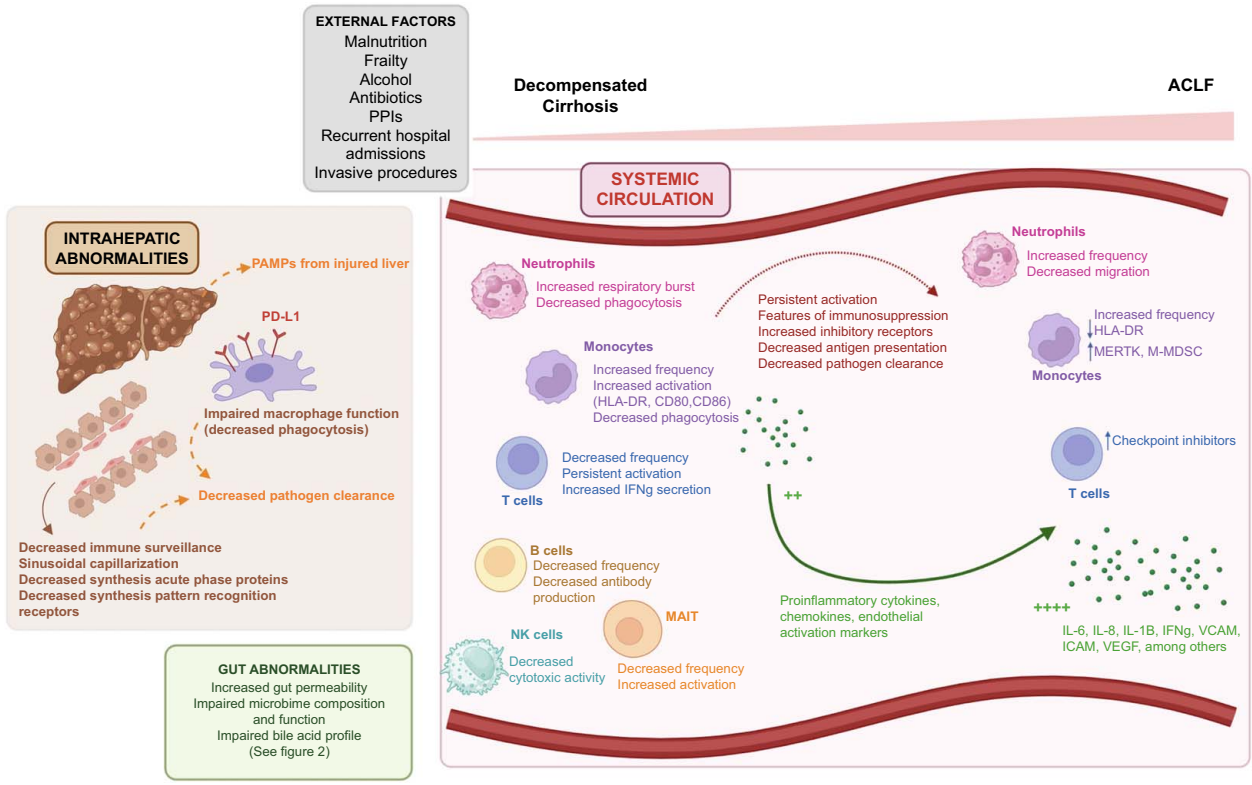

FIGURE 1 Pathogenesis of bacterial infections in cirrhosis: role of cirrhosis-associated immune dysfunction. Each box represents the different compartments involved in the cirrhosis-associated immune dysfunction and the increased risk of infections in cirrhosis. (1) External factors such as malnutrition, excessive alcohol consumption, or frequent hospital readmissions with invasive procedures increase the risk of bacterial infections. (2) Architectural changes in the liver induce impairment of the reticulo-endothelial system and endothelial capillarization that lead to decreased immune surveillance. In addition, KCs (macrophages) have decreased phagocytic function. These intrahepatic changes lead to decreased pathogen clearance that reaches the systemic circulation and activates immune cells. In addition, PAMPs from the injured liver contribute to immune cell activation. (3) Systemic circulation: cirrhosis-associated immune dysfunction affects all circulating immune cell compartments. Overall, innate immune cells show increased activation and decreased phagocytosis and chemotaxis; T lymphocytes are persistently activated and secrete increased levels of IFNg. The knowledge about the impairment of other immune cells is limited. Patients with decompensated cirrhosis have increased levels of proinflammatory cytokines, chemokines, and endothelial factors. All these abnormalities become further impaired in patients with acute-on-chronic liver failure, leading to an exaggerated increase in proinflammatory cytokines, an increase in immunoregulatory cell subsets and features of immunosuppression. Abbreviations: ACLF, acute-on-chronic liver failure; CD, cluster of differentiation; HLA-DR, human leukocyte antigen DR; ICAM, intracellular adhesion molecule 1; IFNg, interferon-gamma; MAIT, mucosal-associated invariant T cells; MERTK, MER tyrosine kinase receptor; M-MDCS, monocytic myeloid-derived suppressor cells; NK cells, natural killer cells; PAMP, pathogen-associated molecular patterns; PD-L1, programmed cell death ligand 1; PPIs, proton pump inhibitors; VCAM, vascular cell adhesion molecule 1.

immunoregulatory populations of monocytes such as monocytic myeloid-derived suppressor cells and MER tyrosine kinase–expressing monocytes[17] and monocytes showing downregulation of HLA-DR.[16,17] The decrease in MHC class II molecules may lead to impaired antigen presentation and T-cell activation. The development of immunosuppressor features is likely due to persistent cell activation and endotoxemia; however, the intimate mechanisms leading to the expansion of immunoregulatory populations need to be elucidated. Given the profound impairment in the innate immune cell compartment, there may be multiple levels of dysfunction. Dendritic cells (DCs) represent the professional antigen-presenting cells and comprise the first step of innate immune activation. However, little is known about DC phenotypes and function in cirrhosis. The role of DCs and whether their function is impaired at any level, from antigen recognition to antigen presentation or immune cell activation, deserves further investigation.

In contrast to the innate immune cell compartment, our knowledge of the adaptive immune response in decompensated cirrhosis is far more limited. Initial studies suggest that adaptive immune response is also impaired, with increased T cells expressing immunosuppressor phenotype and attenuated antigen presentation as cirrhosis progresses.[18] Recent emergent data shows that in patients with decompensated cirrhosis, and particularly in ACLF, there is an increase in T cells expressing programmed cell death protein 1 or T-cell immunoglobulin and mucin-domain 3, checkpoint inhibitors well-known for their role in suppressing immune responses.[19] Characteristics of adaptive immune function in decompensated cirrhosis and their direct effect

TABLE 1 Summary of the abnormalities in immune cell populations and other inherent factors leading to impaired immune responses in cirrhosis

Compartment and cell population/ factors	Abnormalities in decompensated cirrhosis	Further impairment in ACLF (when available)
Systemic circulation		
Neutrophils	Increased respiratory burst. Decreased phagocytosis and chemotaxis.[13,14]	Increased frequency.[15] Decreased migration.[15] Metabolic reprogramming.[15]
Monocytes	Increased frequency. Increased activation (CD80, CD86, and HLA-DR). Decreased phagocytosis and chemotaxis.[10,13]	Decreased HLA-DR, CD80/86 expression; decreased antigen presentation.[16] Increased IL-10 production. Increased immunoregulatory subsets (ie, MERTK and M-MDSC).[17]
Dendritic cells	Limited information; deserves further characterization.	
T cells	Decreased frequency. Increased activation. Decreased antigen presentation.[18,19]	Increased expression checkpoint inhibitors.[19]
B cells	Decreased frequency.[20] Decreased antibody production.[20] Limited information; deserves further characterization.	
NK cells	Decreased cytotoxic activity.[21] Limited information; deserves further characterization.	
MAIT	Decreased frequency. Increased activation markers.[22]	
Systemic inflammation	Increased acute-phase proteins (CRP) Increased proinflammatory cytokines (ie, IL-6, IL-8, IL-1B, and IFNg).[11,12] Increased endothelial activation factors (ie,VCAM, ICAM, VEGF, and vWF).[11,12]	Further increase in acute-phase proteins, proinflammatory cytokines, and endothelial activation factors.
Intrahepatic		
Macrophages/KCs	Decreased frequency. Impaired phagocytic activity. Increased PD-L1, CD163, and others.[23]	
Architectural changes	Porto-systemic shunting. Sinusoidal capillarization. Damage reticulo-endothelial system. Loss cell compartment, increased scar tissue.[10,24]	

Abbreviations: ACLF, acute-on-chronic liver failure; CD, cluster of differentiation; CRP, C-reactive protein; HLA-DR, human leukocyte antigen DR isotype; ICAM, intracellular adhesion molecule 1; IFNg, interferon-gamma; MAIT, mucosal-associated invariant T; MERTK, MER receptor tyrosine kinase; M-MDSC, monocytic myeloid-derived suppressor cells; NK cells, natural killer cells; PD-L1, programmed death ligand 1; VCAM, vascular cell adhesion molecule 1; vWF, von Willebrand factor.

on the increased risk of infections are not completely understood. Whether an increase in checkpoint inhibition reflects immune exhaustion or mere functional T-cell adaptation to persistent activation and may be used as a new target for therapy deserves further study.

At the intrahepatic level, liver macrophages (or KCs) are key in the defense against bacterial infections and have impaired phagocytic activity in advanced cirrhosis.[13,25] A recent, intriguing study showed that the in vivo phagocytic activity of liver macrophages is impaired but can be successfully restored by blocking programmed cell death ligand 1.[23] This raises the question of whether the programmed cell death protein 1/programmed cell death ligand 1 pathway can be targeted for the management of infections in cirrhosis.

Finally, architectural changes in the liver also contribute to immunodeficiency and increased risk of infections. Cirrhosis is associated with damage of the reticulo-endothelial system likely due to the anatomical changes characterized by fibrosis and sinusoidal capillarization and KC loss or damage.[10,24] These abnormalities impair the hepatic immune surveillance and reduce the clearance of bacteria and endotoxin, leading to an increased risk of infections and persistent immune cell activation.[26] Further work is needed to understand the architectural changes as they occur with the progression of stages of cirrhosis and how this contributes to immune dysfunction.

Effects of alterations in gut barrier and microbiome

In addition to the immunologic changes in cirrhosis, the gut mucosa and microbiome also play key roles in infection risk. They provide essential anatomic, physiologic, and ecologic barriers for the translocation of gut microbes. In patients with cirrhosis, it is thought that these barriers are altered and weakened, permitting the translocation of pathogenic gut bacterial species into ascitic fluid and systemic circulation, leading to spontaneous bacterial peritonitis (SBP) and other bacterial infections.[27]

The mucus layers and epithelium are the most important major structures of the anatomic barrier. Mucus layers shield the gut epithelium from the majority of gut microbes, and mucus thinning can precipitate epithelial inflammation and bacterial translocation.[28–30] The gut epithelium is the next major physical barrier. Enterocytes are connected by a network of junctional complexes comprised of tight junctions, adherens junctions, desmosomes, and gap junctions that prevent paracellular translocation of bacteria and macromolecules such as lipopolysaccharides and peptidoglycan.[31] In patients with cirrhosis, altered expression of tight junction proteins claudin-1, claudin-2, occludin, and intracellular scaffold proteins ZO-2 and E-cadherin are thought to mediate epithelial barrier dysfunction, though the mechanisms of pathogenesis are not completely defined.[32–36] In patients with SBP, decreased expression of the tight junction proteins claudin-1 and occludin correlates with severity of cirrhotic decompensation.[31,32] Most recently, it has been found that the gut microbiome can directly impact epithelial integrity, as SBP patient isolates of *Escherichia coli* and *Proteus mirabilis* were found to express matrix metalloproteases that degrade tight junction and scaffold proteins.[36]

Gut epithelial barrier function is also impacted by portal hypertension because congestion of submucous capillaries and veins may directly alter vascular epithelial permeability through altered microcirculation of the intestinal mucosal barrier.[37–39] This hypothesis stems from observational studies of patients with SBP where higher portal pressures and esophageal variceal grade correlate with increased serum inflammatory markers such as lipopolysaccharides and IL-6 and decreased expression of tight junction proteins.[40] The microbiome may also impact portal pressures and liver hemodynamics, as rifaximin therapy was shown to lower the risk for variceal bleed and ascites in a small controlled study.[41]

The intestinal microbiome provides a complementary layer of defense by precluding gut pathogens/pathobionts from accessing the inner mucus layer and epithelium, competing with gut pathogens/pathobionts for nutrients, and secreting metabolites that promote and protect epithelial health.[28] In particular, the short-chain fatty acids, butyrate, acetate, and propionate regulate gut health and permeability.[42–44] Short-chain fatty acids are largely produced by the gut microbiome as they are terminal substrates of carbohydrate fermentation by microbes in the *Faecalibacterium*, *Roseburia*, and *Bacteroides* genera.[43] Butyrate is also produced by microbiome and has been shown to stabilize hypoxia-inducible factor 1 subunit alpha, a transcription factor that promotes the expression of mucin, adaptive, and innate immune responses, and proteins that halt the cell cycle and preserve barrier integrity.[43,45] Acetate, propionate, and butyrate can activate G protein–coupled receptor anti-inflammatory signaling pathways in innate immune cells and prevent the barrier disruption.[43] Recent work has also shown that high levels of short-chain fatty acids decrease colonic pH, which impairs colonization of SBP pathobionts in the *Enterococcus* and *Escherichia* genera.[46,47]

Similarly, the bile acid pool scales with the severity of liver disease and exhibits a relative decrease in the bacterial secondary bile acid forms lithocholic acid and deoxycholic acid.[48,49] This is reflective of a decrease in gut microbes with corresponding chemical functions, such as the Clostridial species, Bacteriodetes, Lactobacilli, and Ruminococcaceae.[50] Overall it is thought that microbiome dysbiosis is impacted by decreased abundance of lithocholic acid and deoxycholic acid, the most potent antimicrobial bile acid forms, which are

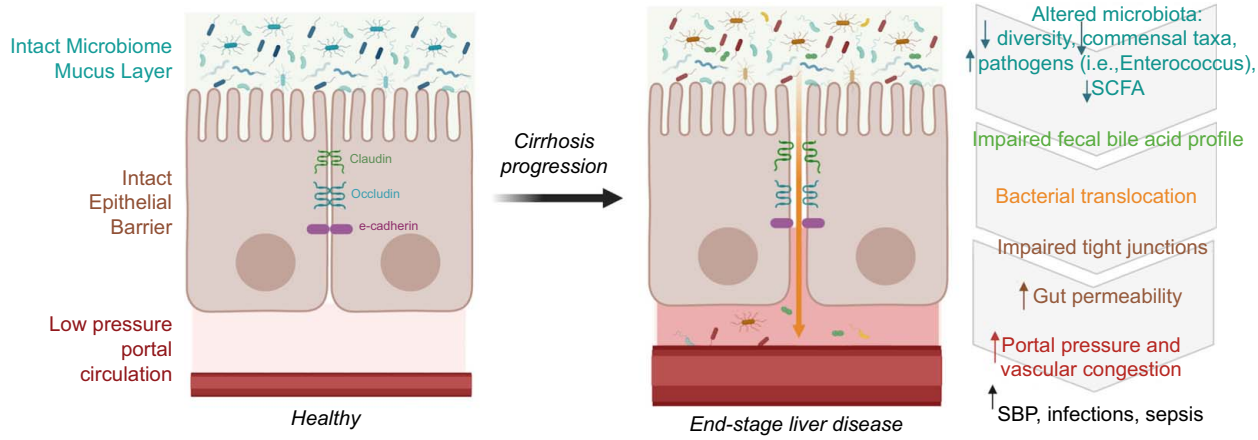

FIGURE 2 Changes in gut barrier and microbiome in cirrhosis. This figure summarizes the key changes in the gut barrier and microbiome that contribute to increasing the risk of infections in cirrhosis. Impaired tight junctions and increased gut permeability lead to increased bacterial translocation. In addition, patients with decompensated cirrhosis show impaired gut microbiome composition and function, with decreased diversity and increased pathogen species. Finally, impaired fecal bile acid composition can also contribute to the impaired gut barrier and immune dysfunction. Abbreviations: SBP, spontaneous bacterial peritonitis; SCFA, short-chain fatty acids.

known to suppress pathogen invasion and pathobiont proliferation.[51,52] Altered bile acid composition may also impact intestinal barrier integrity, liver metabolism, and immune dysregulation through differential signaling of Farnesoid X receptor and Takeda G protein–coupled receptor.[49]

Several studies have shown that Farnesoid X receptor agonists lead to a reduction in bacterial translocation and reduced gut inflammation.[53,54] In addition to its effects on intestinal gut barrier, data derived from patients with liver failure or ACLF suggest that circulating bile acids may also lead to systemic innate immune dysfunction. Depending on their composition and quantity, bile acids may lead to circulating monocyte dysfunction through Takeda G protein–coupled receptor 5 activation.[49]

Is there a microbiome signature for cirrhosis and its complications?

There have been well-characterized associations of gut microbiome configuration with cirrhosis[55,56] and complications such as HE,[57] elevated portal pressure,[58] and acute liver failure.[59] Patients with cirrhosis harbor a distinct stool microbiome signature that can also be measured in serum and ascites, with 89% and 86% overlap at the genus level.[58] Significant increases are seen in Enterobacteriaceae (gram-negative rods, including *E. coli*, *Klebsiella* sp), Enterococcaceae (gram-positive cocci, including *Enterococcus faecalis* and *faecium*), *Streptococcus*, *Fusobacterium*, *Lactobacillus* sp., as well as a general proliferation of oral taxa.[55,56,60] In patients with cirrhosis on antibiotics, these populations can be further increased along with microbes in the Pseudomonadaceae family (including *Pseudomonas aeruginosa*).[61]

Most recently, signatures have been further refined for ACLF and newly shown for SBP. Solé et al[62] performed metagenomic sequencing on 182 patients with cirrhosis, with 65 developing ACLF. In this study, the authors found increases in Enterococcus and Peptostreptococcus genera and saw that loss of gene and metagenomic species richness paralleled the progression of liver disease. These gut microbiome alterations correlated with Child-Pugh scores and organ failure and were associated with HE and infections.[62] A summary of the current known changes in the gut microbiome and metabolites in end-stage liver disease compared to healthy is summarized in Figure 2.

Despite increasing knowledge on each of these areas, further studies are needed to completely understand the mechanisms of the interplay between impaired permeability and microbiome abnormalities that lead to impaired immune responses and increased risk of infections. Changes in microbiome composition lead to differences in the production of microbiome-derived metabolites, which can have a further effect on the gut barrier integrity.[48] The direct role of different cirrhosis-related microbiome signatures or microbiome-derived metabolites on the impairment of the immune response remains to be elucidated.

Alterations of the microbiome highlight a critical area for potential therapeutic and modulation strategies targeting the microbiome to decrease rates of cirrhosis progression as well as infectious complications.

DIAGNOSIS AND PROGNOSIS

Types of infections in cirrhosis

Infections account for a high burden of morbidity and mortality in decompensated cirrhosis.[63] Bacterial

infections occur in 32%–40% of patients with decompensated cirrhosis, manifesting as SBP (20%–35%), bacteremia (8%–21%), urinary tract infection (14%–41%), pneumonia (8%–17%), and soft tissue infection (6%–13%).[64] Bacterial infections in cirrhosis are most frequently caused by Gram-negative bacteria (59%), with the most common organisms being *E. coli* and *Klebsiella pneumoniae*.[6] Gram-positive bacteria are less common, 38% of all infections, with *Staphylococcus aureus* and *Enterococcus* species being the predominant organisms.[6] Fungal infections in cirrhosis are relatively uncommon, making up 3%–7% of culture-positive infections in cirrhosis, with Candida species causing 70%–90% of invasive fungal infections.[6,64] Infections can be community or hospital-acquired, with nosocomial infections associated with a higher risk for mortality than community-acquired infections (25%–58% vs. 7%–21%).[65] Infections are also associated with high rates of sepsis and end-organ failure, 29% and 40%, respectively.[66] Fungal infections are more often secondary infections and nosocomial acquired, with risk factors similar to those in patients without cirrhosis, including central venous catheters, broad-spectrum antibiotics, intensive care unit admission, corticosteroids, and renal replacement therapy.[64] Bacterial infections frequently lead to organ failure in patients with cirrhosis and are the most common precipitating factor of ACLF.[7,8] Almost 50% of patients with cirrhosis and bacterial infections develop ACLF during hospital admission.[9] Mortality rates are further increased with the incidence of MDROs.[6] The high incidence of infections in cirrhosis and high rates of mortality make early and rapid diagnosis critical for optimal management.

Diagnostic tools

Decompensated cirrhosis presents an unusual diagnostic challenge in the diagnosis of infections, particularly sepsis and septic shock. The Sepsis-3 guidelines categorize severity by degree of organ dysfunction and use the Sequential (sepsis-related) Organ Failure Assessment (SOFA) score to predict mortality. A SOFA score of 2 or higher is associated with an in-hospital mortality risk of $>10\%$.[67] A surrogate for SOFA in the outpatient or non–intensive care unit setting is the quickSOFA (qSOFA). Many patients with decompensated cirrhosis may meet these criteria without identifiable infectious etiologies, confounding optimal treatment decisions, such as the need for broad-spectrum antibiotics.

The validation of SOFA and qSOFA scores is limited in patients with cirrhosis. Piano et al[68] assessed the validity of these scoring systems in patients with cirrhosis with a prospective study of 259 patients with cirrhosis and infections. They found that a positive SOFA and qSOFA scores were more accurate in predicting in-hospital mortality than systemic inflammatory response syndrome criteria alone. The difficulty with applying the SOFA and qSOFA scores universally to patients with cirrhosis is their differential underlying degree of organ dysfunction. The European Association for Study of Liver (EASL)-Chronic Liver Failure Consortium (CLIF) modified the SOFA score for patients with cirrhosis in the CLIF-SOFA score, including replacement of platelet count with international normalized ratio and Glasgow coma scale with degree of HE.[69] In any case, both Sepsis-3 criteria and qSOFA should be considered prognostic tools and they have limited utility for ruling in infections.

Additional biomarkers are being studied to help diagnose and prognosticate patients with infections. Pentraxin 3 is expressed by a variety of cells in early inflammation and facilitates activation of the classical complement pathway and macrophage and DCs.[70] Alternatively, IL-6 is a proinflammatory cytokine with mixed data on the diagnostic value for infection in sepsis or end-organ disease. However, Song et al[70] published a prospective controlled study in patients with a positive qSOFA score and found that the diagnostic and prognostic value of IL-6 was superior to both pentraxin 3 and procalcitonin for sepsis and septic shock. In addition, mid-regional pro adrenomedullin is a fragment of adrenomedullin precursor which has vasodilator and natriuretic properties and has been studied for predicting 28-day mortality.[69] The neutrophil-to-lymphocyte ratio is being studied specifically for the diagnosis of infections in cirrhosis and prediction of outcomes, given infections lead to a rise in neutrophil count and suppress lymphocytes.[71] Although there have been concerns about the use of acute-phase proteins, particularly C-reactive protein and procalcitonin, in patients with cirrhosis, there is data showing that they are accurate for the diagnosis of bacterial infections in cirrhosis. However, the accuracy decreases in patients with advanced stages of the disease, probably due to the elevated C-reactive protein levels in patients with no infections.[72] Overall, few studies have specifically evaluated biomarkers as diagnostics for infections, specifically in patients with cirrhosis or ACLF.[73] While these studies show biomarkers are a promising area to aid in the diagnostics of bacterial infections, their usefulness in cirrhosis requires further investigation.

Additional models are being studied to assess mortality in cirrhosis and ACLF. One multicenter study by Bajaj et al[44] assessed admission serum metabolomics to determine effectiveness in predicting mortality. They found that metabolomic profiles, including gut microbial metabolites and hormonal and phospholipid moieties, can predict the development of ACLF as well as 30-day mortality.[44,74]

The use of biomarkers to aid in both diagnostic and prognostic evaluation of infections is rapidly expanding.

Their specific role in patients with cirrhosis requires optimization, given the complex nature of the underlying disease and the role inflammation and microbial products play in driving infection and decompensation. The greatest value would be the use of biomarkers or metabolomic profiles to more rapidly diagnose infections or confidently rule out infection in cirrhosis and ACLF.

MANAGEMENT

MDROs, antimicrobial stewardship

Given the high use of antimicrobials and infection risk in cirrhosis, antimicrobial stewardship is a great concern due to increasing rates of MDROs. In the international study of infections in patients with cirrhosis by Piano et al,[6] the incidence of MDROs was 34% overall, with substantial variation by geographic region, with Asia having the highest rate of MRDOs (50%). Infection by MDROs has been associated with a higher risk of therapeutic failure, septic shock, and in-hospital mortality.[64,75] Risk factors for MDROs identified by Piano et al included the use of systemic antibiotics for at least 5 days in the preceding 3 months, invasive procedures in the previous month, and health care exposure.[6] Interestingly, this study did not find an increase in MRDOs in patients who had received quinolones for SBP prophylaxis.[6] However, other studies have reported an increased risk in MDROs in long-term quinolone prophylaxis with an HR of 2.69.[76] This is a crucial association which requires further investigation, given the number of patients on long-term antibiotics for SBP prophylaxis. Crocombe et al[77] also highlight the evidence to support secondary prophylaxis in SBP, which is limited to reduced risk of SBP but no change in 1-year mortality or overall infection risk. New randomized controlled trials are needed to fully assess the benefits of prophylaxis (for SBP and non-SBP) while quantifying rates of MDROs and mortality in this population.

Fecal microbiota transplant (FMT) has also been studied as a way to reduce antimicrobial resistance genes in the microbiome. Bajaj et al compare 2 small clinical trials of FMT in patients with cirrhosis, which showed a reduction in antimicrobial resistance genes.[78] This may be a viable therapeutic option as antimicrobial resistance genes have been associated with increased mortality.[79] As these studies include small sample sizes, further investigation is needed to determine how FMT could play a therapeutic role in both reducing rates of MDRO infections and/or positive changes in the gut microbiome to reduce infection risk.

Use of albumin

Albumin has been widely used in the management of decompensated cirrhosis and its benefits have been mainly attributed to its oncotic properties. However, there is growing evidence showing that albumin has antioxidant and immunomodulatory properties.[80] Therefore, it is currently believed that the benefits of albumin in cirrhosis go beyond its oncotic properties.

There is a well-established indication for the use of albumin in combination with antibiotics for the management of SBP.[81] A hallmark study showed that the administration of albumin together with antibiotics at days 1 and 3 after diagnosis was associated with a lower risk of acute kidney injury and lower mortality in patients with SBP as compared to antibiotics alone.[82] In contrast, the addition of albumin to antibiotic therapy has shown no benefit in the setting of infections other than SBP.[83–85] The reason for the difference between SBP and non-SBP infections is not completely understood. Whether the difference may be attributed to differences in the population of patients included in the studies (ie, different severity of infections and different severity of underlying cirrhosis) or if it may be related to pathophysiological mechanisms deserves further investigation. Therefore, to date, there is no evidence for the use of albumin in the management of bacterial infections other than SBP.

Finally, there is an ongoing debate on whether repeated doses or long-term administration of albumin may be beneficial in patients with decompensated cirrhosis by decreasing the development of complications and improving survival. Considering that albumin has immunomodulatory properties,[80] the ATTIRE study aimed at investigating whether short-term repeated doses of albumin in hospitalized patients with cirrhosis admitted with decompensation of the disease would decrease the risk of developing bacterial infections, acute kidney injury, and, consequently, improve survival. However, the results of this study did not show differences between the repeated doses of albumin regimen and standard of care.[86] In the outpatient setting, the ANSWER trial showed that long-term administration of albumin improved survival and reduced the incidence of SBP and non-SBP infection.[87] However, considering the open-label design and the negative results of the MACHT trial,[88] further studies are needed to clarify whether the immunomodulatory properties of albumin may provide any further benefit for the prevention or management of bacterial infections.

FUTURE DIRECTIONS

Impact of empiric antibiotics

Current clinical management in ACLF emphasizes the use of empiric antibiotics, which are often continued for a minimum of 7 days or until there is notable clinical improvement. However, the benefits of empiric antibiotics in the setting of negative cultures are limited and

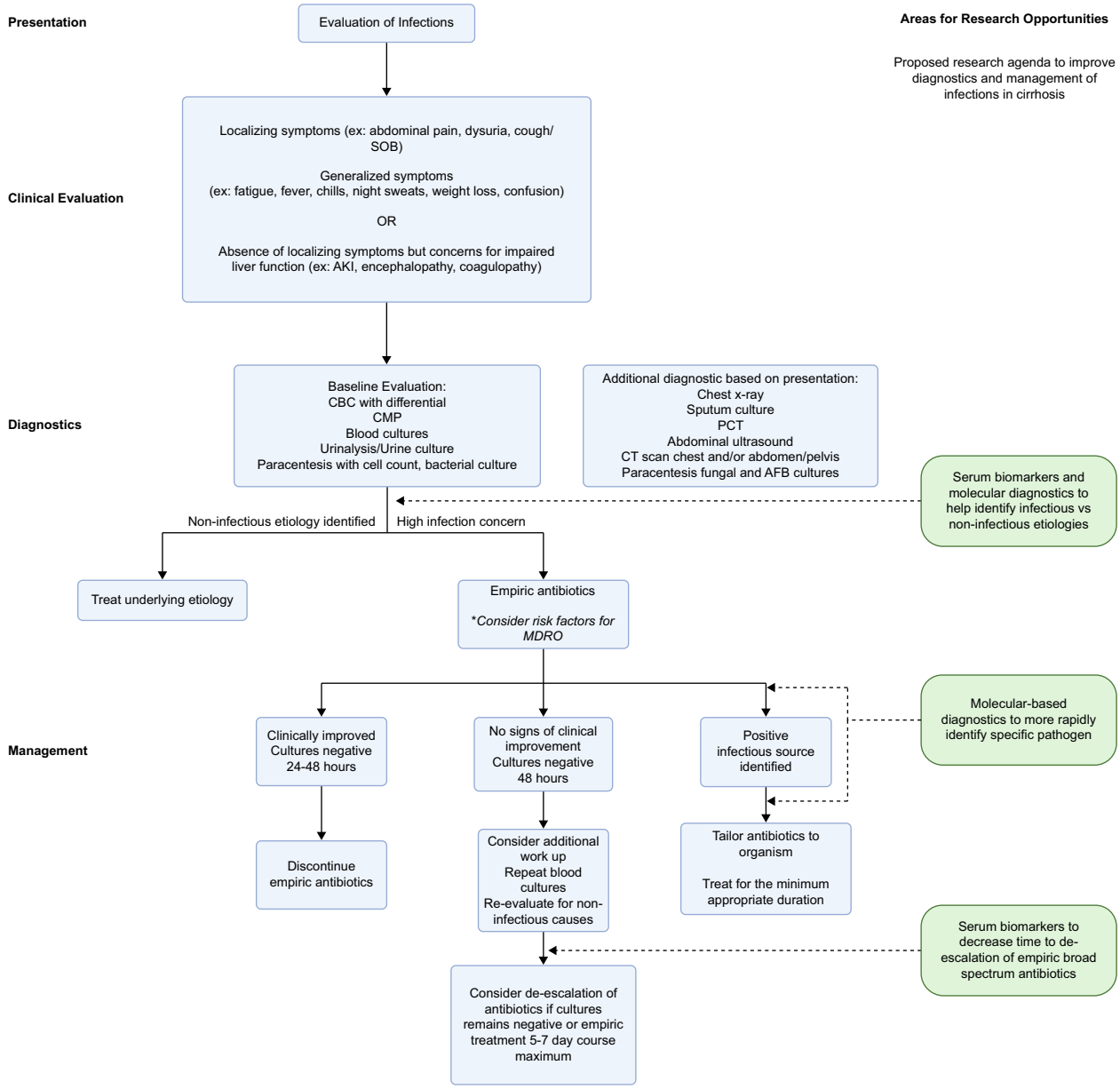
Presentation
Evaluation of Infections
Areas for Research Opportunities
Proposed research agenda to improve diagnostics and management of infections in cirrhosis
Clinical Evaluation
Localizing symptoms (ex: abdominal pain, dysuria, cough/ SOB)
Generalized symptoms (ex: fatigue, fever, chills, night sweats, weight loss, confusion)
OR
Absence of localizing symptoms but concerns for impaired liver function (ex: AKI, encephalopathy, coagulopathy)
Diagnostics
Baseline Evaluation: CBC with differential CMP Blood cultures Urinalysis/Urine culture Paracentesis with cell count, bacterial culture
Additional diagnostic based on presentation: Chest x-ray Sputum culture PCT Abdominal ultrasound CT scan chest and/or abdomen/pelvis Paracentesis fungal and AFB cultures
Serum biomarkers and molecular diagnostics to help identify infectious vs non-infectious etiologies
Non-infectious etiology identified
High infection concern
Treat underlying etiology
Empiric antibiotics
*Consider risk factors for MDRO
Management
Clinically improved Cultures negative 24-48 hours
No signs of clinical improvement Cultures negative 48 hours
Positive infectious source identified
Molecular-based diagnostics to more rapidly identify specific pathogen
Discontinue empiric antibiotics
Consider additional work up Repeat blood cultures Re-evaluate for non-infectious causes
Tailor antibiotics to organism
Treat for the minimum appropriate duration
Serum biomarkers to decrease time to de-escalation of empiric broad spectrum antibiotics
Consider de-escalation of antibiotics if cultures remains negative or empiric treatment 5-7 day course maximum

FIGURE 3 Algorithm for evaluation of infections in cirrhosis. This figure proposes a suggested algorithm for diagnosis and management in patients with cirrhosis with suspected infection. Appropriate diagnostics studies should be ordered on presentation and ensure the infection is identified rapidly given the high risk of decompensation. Empiric antibiotics should be initiated while undergoing diagnostic evaluation if infection is suspected. However, discontinuation of empiric antibiotics or narrowing to organism-specific antibiotics should be expedited to avoid unnecessary antibiotic exposure. Proposed research topics to improve this timeline are summarized on the right. Abbreviations: AKI, acute kidney injury; CBC, complete blood count; CMP, complete metabolic panel; MDRO, multidrug-resistant organisms; SOB, shortness of breath.

further studies on outcomes, including MDROs, are needed. Analysis from the ATTIRE Trial showed half of the patients prescribed antibiotics at the time of study enrollment did not have an infection and showed no benefit in outcomes of 90-day mortality and incidence of hospital-acquired infections after matched-propensity score analysis.[89] Patients prescribed antibiotics had higher MELD scores and higher 28-day mortality, suggesting more severe disease at baseline.[89] Further diagnostics are needed to determine if this represents true noninfectious ACLF or a limitation of current diagnostic testing. Based on the available data, we outline an algorithm to guide appropriate workup and management, and suggest antibiotic de-escalation if no infection is identified (Figure 3).

Advances in rapid diagnostics, including molecular-based studies, use of biomarkers, along with culture data, may be able to improve the time to antibiotic de-escalation if no infection is identified.[90,91] Molecular diagnostics have been successful in antimicrobial stewardship, with one example being the use of methicillin-resistant *Staphylococcus aureus* (MRSA)-nares PCR to discontinue vancomycin for the treatment of pneumonia. One study found that an MRSA-nares

TABLE 2 Potential novel immunomodulatory strategies for the prevention or management of bacterial infections in cirrhosis

Target	Therapeutic strategy	Rationale	Available data
Toll-like receptors	Adjuvants (TLR 7/8, TLR3)	Restore innate immune function (restore cytokine production, phagocytic and antimicrobial activity)	TLR 7/8 restores phagocyte oxidant production and antimicrobial activity in neutrophils (in vitro).[96] TLR3 agonist reduced frequencies of M-MDSC.[99]
PGE2, toll-like receptors	Albumin	In addition to oncotic properties, albumin has immunomodulatory and anti-inflammatory properties.	Albumin modulates TLR signaling in vitro and reduces circulating cytokine levels in patients with AD.[92] Albumin induces a decrease in immunosuppressive PGE2 levels in patients with cirrhosis, leading to restoring macrophage cytokine production [95]
Cytokines	Block cytokine receptors	Reduce immunopathology by reducing cytokine levels	Multiple trials and attempts. Despite potential clinical benefits, blocking cytokines associated with adverse events (ie, increased risk of infections, AKI, and mortality).[95,96]
Stem cells	Induce stem cell mobilization (G-CSF) or stem cell transfusion	Stem cells can differentiate into immune cell lineages and replace dysfunctional immune cells.	G-CSF: mobilizes stem cells from bone marrow. But controversial results from different RCT; not recommended in guidelines.[100–103] Stem cell transplantation: positive results from small trial.[104] RCTs ongoing. Further results required.
MERTK receptor	Block receptors	Restore monocyte function, decrease immunoregulatory subsets	Blocking MERTK restored the production of proinflammatory cytokines in response to LPS.[17]
Checkpoint inhibitors	Block checkpoint inhibitor receptors (ie, anti-PD1, anti–PD-L1).	Restore monocyte/macrophage phagocytic activity and T-cell function	Anti-PD-L1 restored phagocytic activity of intrahepatic macrophages in mouse model.[23] No more available data on patients with cirrhosis; growing evidence in cancer immunotherapy can be used as a starting point to perform further research on cirrhosis.
Gut-liver axis	FXR agonists	Restore intestinal permeability, improve gut barrier dysfunction, and decrease bacterial translocation.	FXR agonists reduce bacterial translocation in animal models.[51,52]

Abbreviations: AD, acute decompensation of cirrhosis; AKI, acute kidney injury; FXR, farnesoid X receptor; G-CSF, granulocyte colony-stimulating factor; LPS, lipopolysaccharide; MERTK, MER receptor tyrosine kinase; M-MDSC, monocytic myeloid-derived suppressor cells; PD1, programmed cell death protein 1; PD-L1, program cell death ligand 1; PGE2, prostaglandin E2; RCT, randomized clinical trial; TLR, toll-like receptors.

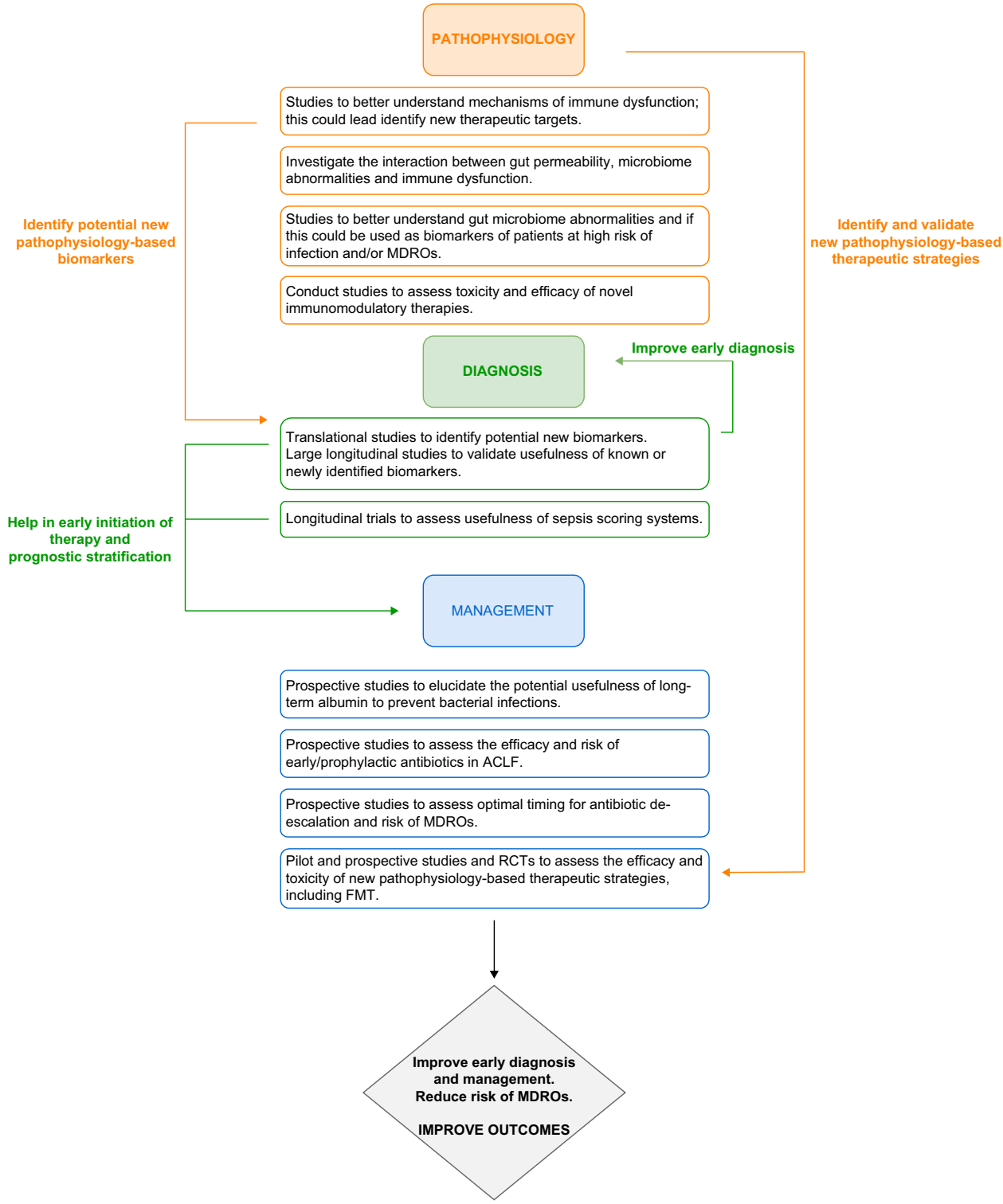
PATHOPHYSIOLOGY
Studies to better understand mechanisms of immune dysfunction; this could lead identify new therapeutic targets.
Investigate the interaction between gut permeability, microbiome abnormalities and immune dysfunction.
Studies to better understand gut microbiome abnormalities and if this could be used as biomarkers of patients at high risk of infection and/or MDROs.
Conduct studies to assess toxicity and efficacy of novel immunomodulatory therapies.
Identify potential new pathophysiology-based biomarkers
Identify and validate new pathophysiology-based therapeutic strategies
DIAGNOSIS
Improve early diagnosis
Translational studies to identify potential new biomarkers. Large longitudinal studies to validate usefulness of known or newly identified biomarkers.
Longitudinal trials to assess usefulness of sepsis scoring systems.
Help in early initiation of therapy and prognostic stratification
MANAGEMENT
Prospective studies to elucidate the potential usefulness of long-term albumin to prevent bacterial infections.
Prospective studies to assess the efficacy and risk of early/prophylactic antibiotics in ACLF.
Prospective studies to assess optimal timing for antibiotic de-escalation and risk of MDROs.
Pilot and prospective studies and RCTs to assess the efficacy and toxicity of new pathophysiology-based therapeutic strategies, including FMT.
Improve early diagnosis and management. Reduce risk of MDROs.
IMPROVE OUTCOMES

FIGURE 4 Research agenda. The algorithm identifies the major unknowns in the topics of pathophysiology, diagnosis, and management of infections in cirrhosis. The unknown topics are used to suggest key areas for future research in this area that can help to improve the identification, management, and outcomes of patients with cirrhosis and infections.

PCR pharmacy-driven protocol led to a 2.1-day reduction in vancomycin use for pneumonia treatment.[92] Reduction in the use of vancomycin is important to reduce the risk of MDROs such as VRE (vancomycin-resistant enterococci). One study evaluating the incidence of VRE-positive cultures in recipients of liver transplant between 6 months before and after transplant showed that patients with VRE had greater vancomycin exposure and were more likely to receive prolonged vancomycin courses. The appropriateness of vancomycin use in

VRE-positive patients was only 26.8%.[93] Given the risk of unnecessary antibiotics, evaluation for infection should be promptly assessed based on symptoms and proper diagnostic evaluation (Figure 3). If appropriate cultures remain negative after 24–48 hours, alternative etiologies to infection should be considered. Further investigation of molecular diagnostics may facilitate more rapid de-escalation in the setting of negative cultures and help to improve antibiotic stewardship and reduce the incidence of MDROs.

Immunomodulatory strategies

Despite increasing knowledge about the main characteristics of cirrhosis-associated immune dysfunction, the key question remains of whether some of these abnormalities can be used as targets for new therapeutic strategies for the prevention or management of infections in cirrhosis. Albumin has shown immunomodulatory properties in vitro.[94,95] However, its beneficial effects in the prevention and management of infections other than SBP are still controversial.[87] Other strategies, such as restoring or enhancing innate immune function by adjuvants that target toll-like receptors or by blocking immunoregulatory receptors (ie, MER tyrosine kinase), have shown beneficial effects in vitro, but further research is needed to confirm whether these options can be beneficial for patients with cirrhosis.[13,96] In the context of exaggerated proinflammatory cytokine levels, targeting cytokines has also been paid a great deal of attention, particularly in the setting of alcoholic hepatitis. However, despite some studies showing potential beneficial results, to date, all trials have failed due to increased adverse events, often related to increased risk of infections.[97,98] Table 2 summarizes available data and potential future perspectives on immunomodulatory strategies for the prevention and management of infections in cirrhosis.

Target gut microbiome abnormalities

More studies are needed to measure the development of cirrhosis-associated microbial signature with disease progression and to understand how the colon and small intestine microbiome facilitate infections in patients with cirrhosis. With further validation, the microbial signature could serve as a predictive marker of disease progression and guide for prophylaxis and therapy, including alteration of disease progression with FMT.

Developing a research agenda

Based on the gaps in knowledge we identified here, we have developed a research agenda that can guide and expedite future investigations in the near future. In Figure 4, we propose key areas of research, ranging from immune dysfunction and gut microbiome abnormalities to prophylaxis, early diagnosis, and management. We hope this agenda will provide the path to generate knowledge with the final goal of improving the management and outcomes of patients with cirrhosis and infections.

CONCLUSIONS

Overall, significant progress has been made to further our understanding of immunologic dysfunction, alterations in the microbiome, risk factors for infectious complications, and predictors of mortality in cirrhosis. However, work is still needed in this arena to improve our understanding of the gut-liver axis and optimize the use of serum biomarkers and empiric antimicrobials, and decrease the risk of MDROs in this vulnerable patient population.

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